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Dissociation dynamics of host-guest interaction between substituted calix[4]-arene and 4-chloronitrobenzene

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The inclusion complexation of upper rim substituted calix[4]arene with neutral 4-chloronitrobenzene has been studied by quantum-chemical and spectrophotometric measurements. The effect of varying temperature on the formation versus dissociation of the host-guest complex has been investigated. The formation of stable host-guest complexes is determined using DFT/B3LYP/ 6-311G(d) level of theory. The π-π interaction based dissociation dynamics of the host-guest complex has been studied. In the host-guest interaction, a 1:1 complex stoichiometry is observed. The low activation energy of dissociation, obtained from the MD simulations, indicates that the complex formation equilibrium is thermodynamically controlled.

Keywords: Supramolecular chemistry, Host-Guest interactions, Density functional calculations, Calix[4]arene, Molecular dynamics,

The development of supramolecular chemistry has led to a growing interest in the design and synthesis of macrocyclic molecules containing intramolecular cavities. In particular, calixarenes have become very popular in supramolecular chemistry in last few years. Calixarenes are often selected as host molecules in sensor research because of their well defined three-dimensional structure with chemically stable intermolecular cavity having coordination selectivity property. These are formaldehyde condensation products capable of binding small molecules into their molecular cavities. Since their introduction of calixarene in 1989 their binding properties have been extensively studied[1,2]. A number of reports have appeared in the literature delineating the versatile properties of calixarenes as capable of forming host-guest complexes not only with cations or anions but also with neutral molecules[3,4]. Hence, they can be used for selective molecular recognition in chemical sensors measuring neutral species also. The studies pertaining to their thermodynamics[5,6] and redox properties[7], applications in analytical and separation science[8], modeling of their molecular dynamics[9,10] and the extent of their metal ion bonding character in solution[11,12] are of great significance.

Molecular dynamics (MD) calculations are the tools to analyze the dynamics process at the molecular level. Literature encompasses a number of MD calculations focused on the complexing behaviour of calixarenes. The quantum-chemical investigations of some calixarene derivatives and neutral π-electron deficient aromatic compounds have also been reported[13-15]. Moreover, the inclusion process is controlled by slight conformational effects. The importance of π-π interactions between the aromatic annulus of calixarene host and neutral guest molecule was recognized as a fascinating capability of this family of macrocycles.

Keeping this in view, it was thought worthwhile to synthesize upper rim substituted calixarene compounds and to explore the effect of varying temperature on the formation versus dissociation behaviour of the host-guest complex. For this purpose 25,26,27,28-tetrahydroxy-5,11,17,23-tetrakis-[4-(4-carboxyl)phenyldiazenyl]calix[4]arene (THPDCA) (**1**) was synthesized (Fig. 1) as the host molecule and the dissociation dynamics of the encapsulated 4-chloronitrobenzene (**2**) as a guest was monitored through MD calculations. The reaction rate constants (*k*) of dissociation of the complex at different temperatures between 273 K and 313 K were calculated. The stoichiometry of the complex formation was determined by spectrophotometery. Quantum-

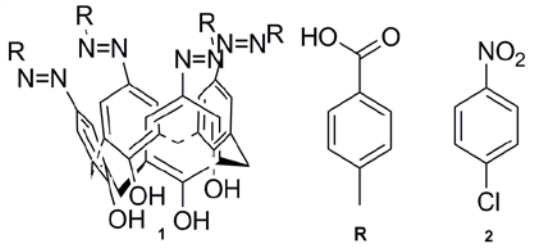


Fig. 1 – THPDCA (1) as host and 4-chloronitrobenzene (2) as guest.

chemical investigations were carried out to determine the stable conformation of the host-guest complex.

Experimental

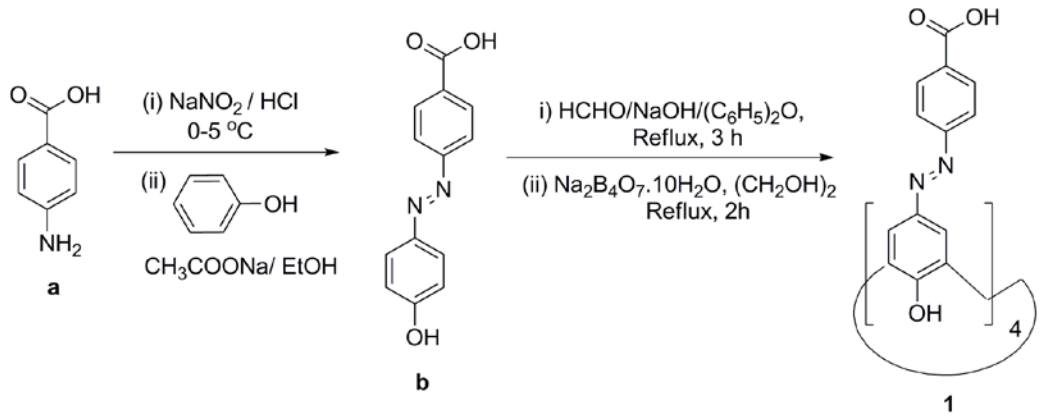
The typical synthesis of THPDCA was achieved in the following sequential steps (Scheme 1). Firstly 4-[(E)-(4-hydroxyphenyl)diazenyl]benzoic acid [b] was prepared as follows: In a 250 mL. beaker, 2.74 g (0.02 mol) of *p*-amino benzoic acid (PABA) in 15.0 mL of concentrated hydrochloric acid and 15.0 mL distilled water were taken. To this, a solution of 1.38 g salt of sodium nitrite in 10.0 mL distilled water was added with constant stirring over a period of 5-10 minutes with temperature maintained in the vicinity of 0-5 ^{o}C. In another beaker, a solution of 1.88 g (0.02 mol) of phenol in 20.0 mL of 10% sodium hydroxide solution was prepared and allowed to cool down to 5 ^{o}C by immersing it in ice bath.

The phenol solution was stirred vigorously, and to this diazotized salt was added very slowly with constant stirring. Orange red crystals of 4-[(E)-(4-hydroxyphenyl)diazenyl]benzoic acid (**3**) appeared soon. It was allowed to stand in ice bath for 30 minutes with occassional stirring, filtered through a Buchner funnel, washed well with plenty of cold water and dried. It was further recrystallized from a mixture of ethanol and acetic acid.

Yield: 88(%); M.pt.: 158-160 ^{o}C, Anal. (%): Calcd for $C_{13}H_{10}N_2O_3$: C, 64.46, H, 4.16, N, 11.56, Found: C, 64.48, H, 4.11, N, 11.49, IR (ν, cm^{-1}): 3450 (-OH), 3015 (C-H, sp^2), 3000-2600 (bs, COOH, characteristic), 1815 (N=N), 1730 (C=O, acidic) 1595, 1489, 1410 (C⋯C, ring str.), 810, 740 (sub. Phenyl). ^{1}HNMR (δ ppm): 7.21-7.63 (m, 8H, Ar-H), 10.42 (s, COOH), 12.52 (bs, -OH). FAB-Mass: 243 (M^++1).

In the second step THPDCA [1] was prepared. Compound (**3**) (4.84 g, 0.02 mol), p-formaldehyde (5.37g, 0.2 mol) and sodium hydroxide (0.27 g, 0.0067 mol) were dissolved in 25.0 mL diphenyl ether in a 250 mL RB flask. The reaction mixture was refluxed for 3 hour under mechanical stirring. It was neutralized with hydrochloric acid and was transferred into a round-bottomed three-necked flask equipped with a mechanical stirrer and thermometer. Then 2.27 g (0.006 mol) of sodium tetraborate decahydrate and 50.0 mL of hot ethylene glycol were added with stirring. The reaction mixture was further refluxed for 2 hours. Then the mixture was cooled down to 80 ^{o}C and poured into 500 mL of cold water. The precipitate obtained was filtered off and dried under vacuum at 50 °C. The dried product was recrystallized from a mixture of chloroform and methanol (4:6, *v/v*).

Yield: 81(%); M.pt.: 212-214 ^{o}C, Anal. (%): Calcd for $C_{56}H_{40}N_8O_{12}$: C, 66.14, H, 3.96, N, 11.02, Found: C, 66.20, H, 3.90, N, 10.95, IR (ν, cm^{-1}): 3525 (-OH), 3040 (C-H, sp^2), 2876 (C-H, sp^3), 2950-2500 (bs, COOH, characteristic), 1814 (N=N), 1732 (C=O, acidic) 1610, 1485, 1391 (C⋯C, ring str.), 910, 815 (sub. Phenyl), 722 (CH_2 rocking). ^{1}HNMR (δ ppm): 3.42 (d, 4H, H_{eq} of Ph-CH_2-Ph), 4.32 (d, 4H, H_{ax} of Ph-CH_2-Ph), 7.12-7.59 (m , 24H, Ar-H), 9.75 (bs, 4H, COOH x 4), 12.52 (bs, 4H, -OH x 4). FAB-Mass: 1018 (M^++1).



Synthetic pathway for the preparation of THPDCA.

Scheme 1

Results and discussion

The initial host-guest geometry for the MD simulations was studied. The stable conformation of THPDCA and 4-chloronitrobenzene were obtained by geometry optimization using DFT/B3LYP/6-311G(d) calculations which describes the hydrogen bonds more accurately and gives shorter OH…O distances that makes the lower rim more closed. Then, the guest molecule was inserted inside the cavity of the host calixarene and the geometry of the complex was further optimized using the DFT/B3LYP/6-311G(d) method. The geometry optimizations for the investigation of the conformers were performed in the Hyperchem 7.0 program[16] by using the Fletcher-Reeves algorithm. The DFT calculations were carried out using Gaussian 09 C.01 program.

Since the aromatic ring of calixarenes can be considered comparatively as electron rich, the electron deficient neutral aromatics were chosen as guest molecules for model studies. Calixarenes and electron-deficient aromatics can form complexes predominantly through π-π type interaction, whilst the inclusion of aliphatic guests into the hydrophobic cavity can be stabilized by CH-π interactions. It was determined using DFT/B3LYP/6-311G(d) geometry and the Langevin MD simulations; the equilibrium conformation of complex of calixarene with neutral aromatic guest molecule is stabilized by π-π interaction. The repulsive coulomb type O-Cl forces are compensated by the attractive forces arising from the possible OH-Cl bonds.

The two opposite rings of the calixarene are nearly parallel and the guest molecule lies between those rings forming a sandwich type structure. The 4-chloronitrobenzene molecule enters into the calixarene cavity and lies between the two opposite aromatic rings of the calixarene framework. Since the phenolic units of calixarene are linked in *ortho* position, the upper part of the guest is more flexible. This property supports the upper part as the entering and leaving channel for the guest molecule during complex formation. Hence, it was found that the interaction of the host with the upper rim of the calixarene has a significant role in the formation as well as the dissociation of the host-guest complex.

The atomic distances between the carbon atoms located at the upper part of the host calix[4] arene (i.e. 25,26,27,28-tetrahydroxy-5,11,17,23-tetrakis-[4-(4-carboxyl)phenyldiazenyl]calix[4]arene (cone conformer) and the carbon atom of the guest (i.e., 4-chloronitrobenzene) are given in Fig. S1 (Supplementary data).

To investigate the stabilization energy of the inclusion complexes, the binding of THPDCA and 4-chloronitrobenzene was examined by quantum-chemical method. The stabilization energy of the complex is the absolute value of the interaction energy, i.e., the difference between the total energy of the optimized structure of the complex and that of the separated host plus guest molecules. The interaction energy between the host and the guest molecules was calculated by the procedure reported earlier[17]. The interaction energy between the host's OH groups and the Cl atom of the guest was found to be 4.6 kJ/mol. Thus, the complex formed is found to be stable. Only those conformations with the *p*-nitrophenol molecule located inside the calixarene cavity (i.e., interacts with calixarene from the side of the upper rim) were found stable. Figure 2 shows the side, top and bottom view of the optimized structure of the host-guest complex.

The dissociation dynamics of the host-guest complex was investigated as a function of the temperature (273-313 K, step: 5 K) by Langevin MD simulations, with the MM+force-field as implemented in the Hyperchem package. First, the 'heating' algorithm was used to reach the desired

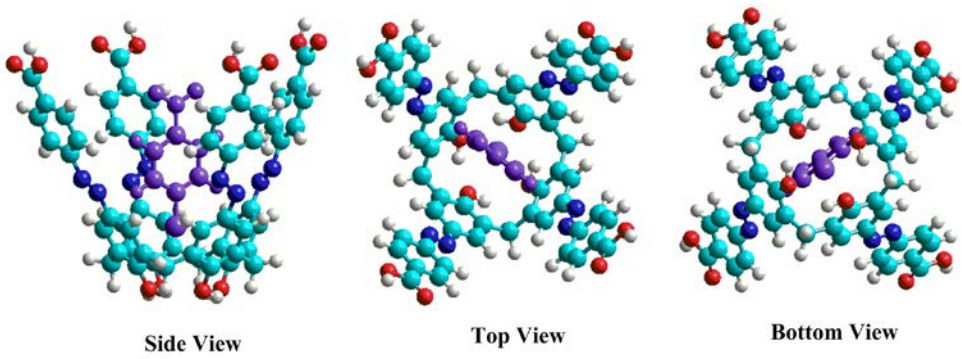


Fig. 2 – Side, top and bottom view of the optimized structures of inclusion complexes of calixarene with 4-chloronitrobenzene.

temperature; this procedure heats up the molecular system smoothly from lower temperatures to the temperature T at which the molecular dynamics simulation is desired to be performed. This heating period was followed by equilibration (few thousand steps) at the given temperature and then, the MD simulations were started. The time step of the simulations was 0.1 fs.

From the MD simulations, the reaction time t was determined as the simulation time until the guest leaves the calixarene cavity[18].

At each temperature, ensembles of N_0=10 trajectories were calculated for a period of 0.6 ps. Thus, reaction rates, k, were calculated by using the relationship,

$$\frac{N}{N_0} = e^{-kt} \qquad \ldots(1)$$

where, t is the reaction time, N_0 is the total number of trajectories and N is the trajectories which did not react. Until the time t, trajectories which do not end with a reaction within the maximum allowed time (0.6 ps) are contributing to the determination of the rate constant (k with dimension s^{-1}) of dissociation by their contribution to number N.

Furthermore, in order to investigate the effect of temperature on the dissociation of the complex, the reaction rate constants (k) were determined at different simulation temperatures between 273 K and 313 K with step of 5 K. The values which vary between 9.9114×10^{13} to 12.8145×10^{13} s^{-1} are summarized in Table 1. A systematic perusal of data reveals that the rate of dissociation increases with the increase of temperature. Hence, the rate of formation and dissociation of the host-guest complex is temperature-dependent.

Table 1 – The calculated reaction rate constants (k) of dissociation of THPDCA complex with 4-chloronitrobenzene at different temperatures between 273 K and 313 K in steps of 5 K

No.	T	k (s^{-1})
1	273	9.9114×10^{13}
2	278	10.4456×10^{13}
3	283	10.7248×10^{13}
4	288	11.3876×10^{13}
5	293	11.8612×10^{13}
6	298	12.0073×10^{13}
7	303	12.1564×10^{13}
8	308	12.5372×10^{13}
9	313	12.8145×10^{13}

By determining the rate constant, the pre-exponential (frequency) factor (A) and the activation energy (E_a) could be calculated by the Arrhenius equation in its linearized form (Eq. 2),

$$\ln k = \ln A - \frac{E_a}{k_B T} \qquad \ldots(2)$$

where k_B is the Boltzmann constant and T is the absolute temperature in Kelvin.

The Arrhenius parameters, i.e., the pre-exponential factor (A) was found to be 7.198×10^{14} kJ/mol and the activation energy (E_a) was calculated as 4.37 kJ/mol. The low value of activation energy of dissociation shows that the complex formation equilibrium is thermodynamically controlled. With a view to express a relationship between rate constants (k) of the dissociation of host-guest complexes and temperature (T), a multiple linear regression analysis was performed and results (Fig. 3) are interpreted in terms of statistical parameters, namely regression coefficient r^2 = 0.970. which were found to be quite promising. On this basis it is clear that rate constants (k) and temperature (T) are fairly well correlated with each other.

The initial conditions and parameters (temperature difference during heating period) and friction coefficient (6 ps^{-1})[19] can influence the results of the simulations of the dissociation dynamics. On the basis of simulation results, it is possible for the guest molecule to remain at the opening of the cavity for longer time (for several ps) which can be attributed to the formation of π- π complex.

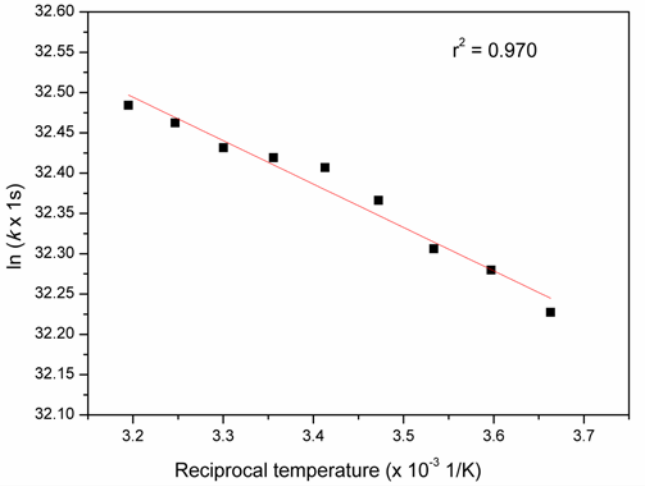


Fig. 3 – Arrhenius plot of the rate constants of the dissociation of host-guest complexes: **1** with **2**.

In order to determine the stoichiometry of the complex formation, 2.0×10^{-4} *M*, stock solution of guest [G] and host [H] were mixed in six different [H]/([G]+[H]) ratios by stepwise addition of $n \times 200$ μL host to $(5\text{-}n) \times 200$ μL guest solutions (n = 1, 2, 3, 4, 5), keeping 2.0×10^{-4} *M* total concentration ([G]+[H]). The Job's curve showed a peak at 0.5 indicating 1:1 complex stoichiometry. Stoichiometry of the complex formation was determined by Job's method using PharmaSpec 1700 UV-vis spectrophotometer.

The present study shows the significant role of the upper rim of the calixarene in the dissociation of the complex and the temperature dependence of the reaction rate. In line with these findings, from the Job's method using spectrophotometry, 1:1 complex stoichiometry was obtained. The low activation energy of dissociation, obtained from the MD simulations, indicates that the complex formation equilibrium is thermodynamically controlled. The π-π interaction based dissociation dynamics of the complex of THPDCA with the 4-chloronitrobenzene was investigated. The results of the above study can contribute to the development of selective and sensitive sensing probes for chemical entities vis-a-vis in designing of efficient molecular vessels for small aromatic compounds.

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Supplementary data

Supplementary data associated with this article, viz., Fig. S1, is available in the electronic form at http://www.niscair.res.in/jinfo/ijca/IJCA_55A(03)304-308_SupplData.pdf.

References

1 J M Lehn, J L Atwood, J E D Davies, D D McNicol and F Vogtle, *Comprehensive Supramolecular Chemistry* edited by (Pergamon, Elsevier Science, Oxford) 1996.
2 Gutsche C D, *Calixarenes*, (Royal Society of Chemistry, Cambridge) 1989.
3 Bohmer V, *Angew Chem Int Ed Engl*, 34 (1995) 713.
4 Kunsági-Máté S, Csók Z, Iwata K, Szász E & Kollár L, *J Phys Chem B*, 115 (2011) 3339.
5 Gutsche C D, *Monograph in Supramolecular Chemistry*, *Vol. 1. Calixarene*, (The Royal Society of Chemistry, Cambridge) 1983.
6 Kunsági-Máté S, Lecomte S, Ortmann E, Kunsági-Máté É & Desbat B, *J Incl Phenom Macrocycl Chem*, 66 (2010)147.
7 Gutsche C D, *Monograph in Supramolecular Chemistry*, *Vol. 6. Calixarene Revised*, (The Royal Society of Chemistry, Cambridge) 1998.
8 Mohammed-Ziegler I & Grun A, *Spectrochm Act A*, 62 (2005) 506.
9 Daniel de Namor A F D, Cleverly R M & Zapata-Ormachea M L, *Chem Rev*, 98 (1998) 2495.
10 Beer P D, Gale P A & Chen G Z, *J Chem Soc Dalton Trans*, 12 (1999) 1897.
11 Ludwig R & Fresenius J, *Anal Chem*, 367 (2000) 103.
12 Varnek A & Wipff G J, *Comput Chem*, 17 (1996) 1520.
13 Lauterbach M, Wipff G, Echegoyen L & Kaifer A, *Physical Supramolecular Chemistry*, (Kluwer Academic Press, Dordrecht, The Netherlands) 1999.
14 Ikeda A & Shinkai S, *Chem Rev*, 97 (1997) 1713.
15 Barroso-Flores J, Silaghi-Dumitrescu I, Petrar P M & Kunsági-Máté S, *J Incl Phenom Macrocycl Chem*, 75 (2013) 39.
16 *Hyperchem (TM) Prof 7*, (Hypercube, Inc.: Gainesville, Florida).
17 Kunsági-Máté S, Nagy L, Nagy G, Bitter I & Kollár L, *J Phys Chem B*, 107 (2003) 4727.
18 Lemli B, Peles J, Kollár L, Nagy G & Kunsági-Máté S, *Supramol Chem*, 18 (2006) 251.
19 Ramachandran G & Schlick T, *Phys Rev*, E 51 (1995) 6188.